Attorney Docket No. 5051-574CT PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Martin et al.
Serial No.: 10/802,644
Filed: March 17, 2004
For: *Blocking Peptide for Inflammatory Cell Secretion*

Confirmation No.: 3963
Art Unit: 1644
Examiner: Haddad

Date: July 11, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attachment B

Declaration of Duncan Rogers, Ph.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No: 5051-574CT

In re patent application of

Linda D. MARTIN *et al.*

Group Art Unit: 1644

Serial No. 10/802,644

Examiner: Maher M. Haddad

Filed: March 17, 2004

For: BLOCKING PEPTIDE FOR INFLAMMATION SECRETION

DECLARATION UNDER 37 C.F.R. §1.132

I, Duncan Fraser Rogers, declare that:

1. I hold the academic position of Reader in Respiratory Pharmacology and administrative position of Director of Postgraduate Studies (Research) at the National Heart & Lung Institute, Imperial College London, UK. I hold a PhD in Physiology (University of London) and am a Fellow of the Institute of Biology (UK). I have worked in the field of respiratory physiology and associated pulmonary diseases for over 25 years (from 1980 to the present). A copy of my Curriculum Vitae is appended hereto as **Exhibit 1.**

2. I have read and understood the rejections made in the Office Action in the above-captioned application, mailed on January 11, 2006 and I reviewed the presently pending amended claims. Specifically, the Examiner stated that "the state of the art is that current treatments of diseases associated with airway mucus hypersecretion, such as cystic fibrosis, asthma, and bronchitis, do[es] not take into account the homeostatic role of pulmonary mucus, and the impact of mucus on respiratory pathophysiology." The Examiner then refers to the Rogers 2003 publication as suggesting that "optimal treatment should aim at the reversion to normal levels of secretion rather than merely to inhibit hypersecretion." I am the sole author of the Rogers cited publication, referred to above as "Rogers (2003)," and specifically known as *Pediatric Pulmonology* 36: 178-188 (2003) (hereinafter referred to as "Rogers 2003"), and I would like to comment on the Examiner's interpretation of my publication. However, I find it puzzling that the Examiner refers to my publication and Dr. Barnes' 2002 publication as supportive of the Examiner's characterization of the state of the art when it is my understanding

that the claimed ~~in vivo~~ methods are directed to inhibiting the MARCKS-related release of an inflammatory mediator by the administration of the MANS peptide. In the claimed methods, MANS peptide inhibits the MARCKS-related release of inflammatory mediators whereas my and Dr. Barnes' publications are directed to the study of treatments of airway mucus hypersecretion. Persons skilled in the study of respiratory physiology and the associated pulmonary diseases, such as myself, would know that mucus hypersecretion does not cause inflammation of the airways, and therefore, we would not find these publications particularly relevant regarding the state of the art in inhibiting the release of MARCKS related inflammatory mediators in a subject suffering from inflammation.

However, since the Examiner has raised my disclosure in Rogers 2003 as being supportive of his position of lack of enablement, I would like to provide my comments. By way of clarification, it is my opinion that it is understood by researchers and physicians within the pulmonary field that a normal level of mucus secretion is important for entrapment of inhaled particles in the mucus gel layer and removal from the airways by mucociliary clearance which provide protective benefits (see Rogers 2003, page 179). However, it is also clear that airway mucus hypersecretion can be detrimental to patient health and needs to be treated. Therefore, I believe that persons skilled in the field would understand that mucus inhibition treatment should not inhibit all mucus secretion but rather only inhibit mucus hypersecretion that is excessive and which results in pathophysiological effects on the airway. The correct dosage of drug would be determined in appropriate clinical trials, initially in Phase I trials, and subsequently becoming more refined for clinical use in Phase II and Phase III trials. This procedure holds true for any potential new drug for human use, not just drugs for anti-mucus therapy in the airways. Based upon these trials, skilled persons would be able to determine an appropriate dosage of mucus hypersecretion inhibitor to administer to persons with respiratory diseases that are characterized by mucus hypersecretion.

3. Similarly as noted above, I do not find publications on current treatments of diseases associated with airway mucus hypersecretion to be relevant to the assessment of the state of the art associated with inhibiting MARCKS-related release of inflammatory mediators. But since the Examiner has referred to a publication by my colleague, Dr. Peter J. Barnes entitled "Current and future therapies for airway mucus hypersecretion," as suggesting that "the clinical

benefits from inhibiting mucin hypersecretion are still not certain, casting some doubts on this therapeutic approach," I also wish to comment on the Examiner's interpretation of this publication. Generally, persons skilled in the pulmonary field have either performed experiments or have analyzed peer reviewed scientific publications that provide evidence that the inhibition of excessive mucus secretion or hypersecretion does result in the alleviation of some or all symptoms which are known to characterize respiratory diseases. Thus, it may be seen that there are specific and identifiable reasons why I view inhibition of airway mucus hypersecretion as a valid therapeutic target in both COPD (Rogers 2003, page 184) and asthma (Rogers, 2004 – **See Exhibit 2**). I see anti-MARCKS therapy as a logical and legitimate approach to reducing airway mucus hypersecretion in these conditions. It is also feasible that anti-MARCKS therapy would have clinical benefit in CF and bronchiectasis. It is noteworthy that even though Barnes (2002) states in the abstract that clinical benefits from inhibiting mucus hypersecretion are still not certain (in the absence of clinical trials), Barnes (2002) also identifies MARCKS inhibitors as potential treatment for airway mucus hypersecretion in COPD, and possibly from multiple causes (pages 245 – 246). The Rogers (2003, 2004) and Barnes (2002) articles cite the high-impact factor journal paper by Li *et al* 2002 (with Adler as senior author - **See Exhibit 3**.) as evidence for their assertion that anti-MARCKS therapy for airway mucus hypersecretion merits consideration. A subsequent paper from Adler and colleagues (Nature Medicine 2004, 10, 193-196) (**See Exhibit 4**.) has extended the original observations, and confirms that Rogers and Barnes were correct in supporting a role for anti-MARCKS therapy for airway mucus hypersecretion. But again, these publications say nothing about the inhibition of MARCKS-related release of inflammatory mediators, and therefore, are not relevant to show the state of the art for the claimed invention.

4. I also have read the abstract by Adler *et al.* (CHEST 2000: 117: 266S-267S) and read the Examiner's comments in the Office Action beginning on page 7. The first sentence in the Adler abstract does not suggest to me that inhibition of mucus hypersecretion will inhibit inflammation in the airways because to my knowledge, mucus hypersecretion does not have a direct effect on inflammation. In fact, although inflammation and a myriad of inflammatory and immune mediators could affect mucus production and possibly secretion, interpreting this sentence as claiming that mucus can cause inflammation, or even suggesting that mucus can

directly cause inflammation is absolutely incorrect. There is no scientific basis for such an assertion. As stated by Adler (CHEST 2000: 117: 266S-267S), "Hypersecretion of mucus contributes to airway inflammation and obstruction ..." My reading of this is that there is no indication that mucus causes inflammation, and is certainly not stated as such by Adler.

A further example of the lack of evidence that mucus causes inflammation directly is found in Fischer and Voynow from CHEST 2000; 117:317-320S **(Exhibit 5)**, which discloses "Airway diseases such as cystic fibrosis, chronic bronchitis, and viral- or pollution-triggered asthma have two common pathologic features: mucus obstruction of the airways, and neutrophil-predominant airway inflammation. Neutrophils release high concentrations of elastase (neutrophil elastase [NE]), a serine protease, into the airways; exposure to elastase results in secretory metaplasia and increased production/secretion of mucin glycoproteins. We have previously shown that NE increases gene expression of a respiratory mucin, *MUC5AC*, in both A549, a lung adenocarcinoma cell line, and cultured normal human bronchial epithelial cells." (see abstract). This suggests that an inflammation mechanism can produce mucin hypersecretion (the mechanisms are related in this cause and effect direction), but does not demonstrate or even suggest the reverse dependency.

Additionally, one skilled in the art would realize that inflammation can occur in essentially every tissue and organ in the body, the majority of which do not produce or secrete mucus, and inhibition of release of inflammatory mediators by inflammatory cells via administration of a MARCKS-related peptide in these tissues clearly has no relationship to mucus in any sense.

The Adler abstract presents a study of the mechanism whereby mucus hypersecretion is inhibited by a synthetic peptide identical to the myristoylated N-terminal region of the MARCKS protein. There is no mention of the effect of this peptide on inflammation in the airway. Further, there is no information regarding how the MANS peptide would inhibit the release of any inflammatory mediators. Therefore, a person skilled in the art, such as myself, would not be motivated by this abstract, to inhibit MARCKS-related release of inflammatory peptides, by administering the MANS peptide.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made

are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

7th July 2006
Date

Duncan Fraser Rogers, Ph.D.